

REMARKS

The 35 U.S.C. §112 Rejections

Claims 16-18 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. This rejection is respectfully traversed.

Claim 16 stands rejected because the claim recites "said single chain antibody" without antecedent basis. Claim 16 has been amended. The Applicant respectfully requests that the rejection of claims 16-18 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim 18 stands rejected under 35 U.S.C. §112, first paragraph, as not enabled. This rejection is respectfully traversed.

The Examiner has rejected claim 18 because the specification fails to show that the cell line producing scFv-23 is known and readily available to the public or has been deposited by the inventor. The scFv-23 single chain antibody will be available as Applicants will deposit a cell line producing scFv-23. Accordingly, the Applicant respectfully requests that the rejection of claim 18 under 35 U.S.C. §112, first paragraph, be held in abeyance.

The 35 USC §103 Rejections

Claims 15 and 19 stand rejected under 35 USC §103(a) as unpatentable over **Rosenblum** (Cancer Communication, 1991) in view of **Hudziak** (Molecular and Cellular Biology, 1989). This rejection is respectfully traversed.

The Examiner argues that it would be obvious to use the method of **Rosenblum** to conjugate TNF to an anti-p185^{HER2}/anti-erbB2 monoclonal antibody to obtain the enhanced cytotoxic effect observed in the instant invention. The Applicants respectfully disagree.

While **Rosenblum** describes the conjugation of tumor necrosis factor to monoclonal antibody against a melanoma cell specific 240 kDa glycoprotein, this is an entirely different antigen than that of the instant invention. **Hudziak** reports that unconjugated monoclonal antibody against p185^{HER2}/anti-erbB2 sensitizes breast cancer cells to unconjugated tumor necrosis factor. However, this requires the separate administration of the antibody

and tumor necrosis factor.

The instant invention improves on **Hudziak** by administering TNF concurrently with the sensitizing antibody. This is more effective and specific than separate administration of each entity. However, one skilled in the art could not determine from the combination of **Rosenblum** and **Hudziak** whether tumor necrosis factor conjugated to an anti-p185^{HER2}/anti-erbB2 antigen would be still be effective against the target cells. It is possible that the conjugation event might disrupt the domains of the TNF moiety essential to its function. Alternatively, the binding site of the antibody might be blocked in the conjugate eliminating the specific targeting of the resulting conjugate. Time-consuming, non-routine experimentation, beyond that which is obvious to one skilled in the art, would be required to determine if the anti-p185^{HER2}/anti-erbB2-TNF conjugate would exhibit the same effect as the separate administration of each component. Therefore, the applicants respectfully request that the rejection of claims 15 and 19 under 35 USC §103(a) as obvious over **Rosenblum** in view of **Hudziak** be withdrawn.

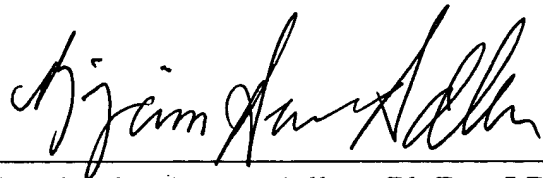
Claims 16 and 17 stand rejected under 35 USC §103(a) as unpatentable over **Rosenblum** (Cancer Communication, 1991) in view of **Hudziak** (Molecular and Cellular Biology, 1989) in further view of **Bird** (1988). This rejection is respectfully traversed.

Bird describes the formation of single-chain antigen binding proteins. However, **Bird** discusses neither a monoclonal antibody against p185^{HER2}/anti-erbB2 nor tumor necrosis factor. Therefore, nothing in **Bird** resolves any of the inadequacies relative to the instant invention in the combination of **Rosenblum** and **Hudziak**. While **Bird** may enable the formation of single chain antigen-binding protein from the monoclonal antibody of the instant invention, the combination of **Bird**, **Rosenblum** and **Hudziak** still fails to show that conjugation of the single chain antibody to tumor necrosis factor would result in a conjugate effective against the target cells. Therefore, the Applicants respectfully request that the rejection of claims 16 and 17 under 35 USC §103(a) as obvious over **Rosenblum** in view of **Hudziak** and in further view of **Bird** be withdrawn.

This is intended to be a complete response to the final Office Action mailed April 26, 2000. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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